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EXAMINER
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ART UNIT	PAPER NUMBER
1642	6

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/884,001	Bird et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 15, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *53-77* is/are pending in the application.

4a) Of the above, claim(s) *53-58 and 64-77* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *59-63* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed December 16, 2002 (Paper No. 5) in response to the Office Action of July 15, 2002 (Paper No. 3) is acknowledged and has been entered. Claims 53-77 are pending in the application and Claims 53-58 and 64-77 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 59-63 are currently under prosecution.

2. Applicants election, with traverse, of Group V, claims 61-63 is acknowledged. The traversal is on the ground(s) that the invention of Group IV, claims 59-60 are drawn to a polypeptide encoded by SEQ ID NO:1. Applicant points to page 5 line 32-page 6 line 1 wherein it is shown that SEQ ID NO:1 encodes SEQ ID NO:2. The argument is persuasive and Groups IV and V are hereby rejoined. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement drawn to Groups I-III and VI-XI, the election of rejoined groups IV and V is now treated as an election without traverse (MPEP 818.03(a).

3. It is noted that the Information Disclosure Form submitted by Applicant on 1/21/03 has not been signed and that the references have not been considered because Examiner does not have access to Pct/US99/29989. Submission of the references cited in the IDS could be appreciated.

Specification

4. The specification is objected to because of typographical errors, for example, "Inhibitors or sGNK phosphorylation" recited on p. 9, line 26.

Appropriate correction is required.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reasons(s) set forth on the attached Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, sequences are recited on p. 15, lines 24-25 and on page 20 lines 30-31 which are not associated with a unique sequence identifier. The sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids. The rules apply to all sequences in a given application, whether claimed or not (See MPEP 2421.02). Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where there informalities may be found. Appropriate correction is required.

Claim Objections

6. Claims 59 and 60 are objected to because they are dependent upon a non-elected claim. The rejection can be obviated by the claims to include the limitations of the claims from which they depend.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 59-63 are rejected under 35 USC 101 because the claimed invention is not supported by either a well established utility or a substantial utility.

The disclosed utilities for sGNK, SEQ ID NO:2, include its use as a purification reagent, as a reagent for measuring biological activity, identification of agonists or antagonists, identification of unknown proteins, antigen for the formation of antibodies and its use as a therapeutic agent (p. 35, lines 25-33). However, neither the specification nor any art of record teaches what sGNK is, what it does do, they do not teach a utility for any of the 80% variants claimed or polypeptides comprising fragments of SEQ ID NO:2, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for sGNK, such as its use as a purification reagent, as a reagent for measuring biological activity, identification of agonists or antagonists, identification of unknown proteins, antigen for the formation of antibodies to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities Other than its phosphorylation, *in vitro* by GNK, no other functional property of SEQ ID NO:2 is taught. An additional disclosed utility for sGNK is its use as a therapeutic agent. This asserted utility for sGNK appears to be based on the assertion that sGNK is phosphorylated by GNK *in vitro* and co-purifies with GNK (p. 9, lines 22-25). GNK defective fetuses displayed reduced vascularization in the yolk sac and placenta. The specification hypothesizes that this finding in an animal model indicates that GNK plays a critical role in angiogenesis and vascular biology (p. 8, lines 19-22). Given that hypothesis, the specification suggests that sGNK also plays a critical role in angiogenesis and that it

is useful for treating diseases associated with angiogenesis. The specification further hypothesizes that given the copurification of the two proteins, the proteins **may** (emphasis added) form a higher-order complex. Thus activators and inhibitors of sGNK **may** (emphasis added) thus be useful in enhancing or decreasing angiogenesis. Clearly, the claimed invention does not have substantial utility because additional work is required in order to determine whether or not sGNK does in fact form a higher-order complex with GNK, is in any way involved with angiogenesis or is in any way associated with any disease state. In addition, the "critical role" pf GNK in angiogenesis and vascular biology is based on the vascular defects in GNK deficient mice, wherein the deficiency was lethal at approximately embryonic day 11.5 (p. 50, lines 1-10). However, it is not possible to correlate this information with the utility of the instant invention because there is no guidance either in the specification or in the art of record that any human has ever been identified any disease or condition that was in any way associated with the GNK enzyme or with its putative substrate sGNK. It is notoriously well known in the art that humans are different from the species of mice used for transgenic research in that the mice are much more tolerant of mutations than are humans. Given the lethality of the GNK mutation (that is the loss of both alleles) it would be expected that loss of GNK or its mutation would be embryonically lethal in man as well. No association of GNK with any disease or condition associated with vascularization or angiogenesis in humans has been disclosed. Further experimentation would be required in order to determine if either GNK or sGNK is in fact mutated in humans and then to determine whether of not the mutation is associated with any condition

or disease associated with angiogenesis or vascularization, thus the claimed sGNK does not have substantial utility or a well established utility. As disclosed above, the specification states that activators and inhibitors of sGNK **may** (emphasis added) be useful in enhancing or decreasing angiogenesis. Although the specification states that inhibitors of sGNK phosphorylation will block subsequent biological activities of the protein such as interfering with cell division or differentiation or blocking a signal pathway and that activators of sGNK are expected to enhance its biological properties (p. 9, .lines 24-29), it is clear that Applicant recognizes that further experimentation is required to characterize the function of the protein and that there is no well established utility for the protein. Again, neither the specification nor any art of record teaches what sGNK is, what it does do, they do not teach a utility for any of the claimed 80% variants or the polypeptides comprising fragments of SEQ ID NO:2, do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases.

The specification further states that sGNK shows a high degree of sequence homology with the Bicaudal-D gene of Drosophila. The Bicaudal-D gene encodes a cytoskeleton-like coiled coil polypeptide with a leucine zipper and five alpha helix domains. Mutations in bicaudal-D disrupt the cytoskeleton, interfere with mRNA sorting and disrupt the polarity of the developing embryo (p. 9, lines 6-11). Since the specification repeatedly states that sGNK is associated somehow with vascularization and angiogenesis, it would not be expected that the homology to the Bicaudal-D gene of Drosophila could be extrapolated to the function of that sGNK because the functions of the claimed protein and bicaudal-D are clearly different.

This is not surprising since a database search revealed that SEQ ID NO:2 has a 39% best local similarity to 32.5% of bicaudal-D, that is a homology of 12.4% between the two proteins (see Sequence Data Report us-09-884-001-2.rsp, result 1, attached). Given the teaching in the art, it is not clear why Applicant states that sGNK shows a high degree of sequence homology to Bicaudal-D gene product. In addition, the specification teaches that sGNK also contains a region that is highly homologous to C-Nap1, a novel centrosomal coiled coil protein that appears to be the substrate of Nek 1 (p. 9, lines 13-22). However, the specification does not disclose the degree of identity of NAP-1 and sGNK and a search of the SPTREMBL_21, , BLOSUM62 and GENESEQ_101002 databases did not reveal any identity between NAP-1 and SEQ ID NO:2, although the identities reported went from 100% identity to 7.9% identity. It would not appear that an identity between the two proteins is substantial or that the activity or function of NAP-1 could be extrapolated to sGNK. Thus, the claimed sGNK does not have a well established identity based on sequence homology to either bicaudal-D or NAP-1. Given the above, neither the specification nor any art of record teaches what sGNK is, what it does do, do not teach a relationship to any specific diseases or conditions or establish any involvement in the etiology of any specific diseases The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed protein. Because the claimed invention is not supported by a specific utility, a well established utility, a substantial utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

10. Claims 59-63 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

11. If Applicant were able to overcome the rejections under 35 USC 101 and 35 USC 112, first paragraph above, Claims 59-63 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising SEQ ID NO:2, does not reasonably provide enablement for an isolated polypeptide with at least 80% identity to SEQ ID NO:2, wherein the polypeptide is capable of binding to and/or being phosphorylated by GNK or a polypeptide produced from a polynucleotide that is capable of hybridizing to SEQ ID NO:4 under conditions of moderate stringency, polypeptides comprising fragments of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to an isolated polypeptide with at least 80% identity to SEQ ID NO:2, wherein the polypeptide is capable of binding to and/or being phosphorylated by GNK or a polypeptide produced from a polynucleotide that is capable of hybridizing to SEQ ID NO:4 under conditions of moderate stringency as well as polypeptides comprising fragments of SEQ ID NO:2 that will bind to or can be phosphorylated by SEQ ID NO:4. The specification teaches that sGNK is a substrate of GNK *in vitro* and co-purifies with GNK (p. 9, lines 22-25). SGNK shows a high degree of Sequence homology with the Bicaudal-D gene of Drosophila. The Bicaudal-D gene encodes a cytoskeleton-like coiled coil polypeptide with a leucine zipper and five alpha helix domains. Mutations in bicaudal-D disrupt the cytoskeleton, interfere with mRNA sorting and disrupt the polarity of the developing embryo (p. 9, lines 6-11). Further, sGNK also contains a region that is highly homologous to C-Nap1, a novel centrosomal coiled coil protein that appears to be the substrate of Nek 1 (p. 9, lines 13-22). The invention also encompasses fragments of Seq ID NO:2 comprising at least 20 or at least 30 contiguous amino acids of SEQ ID NO:2 (p. 14, lines 10-11).

One cannot extrapolate the teaching of the specification to the scope of the claims because even if it were to be determined that sGNK activity is the same as that of Bicaudal-D or C-NAP1 to which the specification discloses identity, it is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. In particular, given the broad scope of the claims, that is that the claims are drawn to a polypeptide that is at least 80% identical to sGNK, a polypeptide encoded by a nucleic acid molecule that is capable

of hybridizing at conditions of moderate stringency to SEQ ID NO:1 (which reads on nucleic acid molecules that encode polypeptides with little or no homology to SEQ ID NO:2), polypeptides comprising unspecified fragments of SEQ ID NO:2, the effects of these differences in amino acid sequence between the broadly claimed polypeptides and SEQ ID NO:2 cannot be predicted. For example, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in

transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with at least a 20% or more dissimilarity, to SEQ ID NO:2, the function of the SEQ ID NO:2 homologue could not be predicted, based on sequence similarity with Bicaudal-D or with C-NAP1, nor would it be expected to be the same as that of Bicaudal-D or C-NAP1. In addition, it is clear that the broadly claimed polypeptide encoded by a gene that hybridizes under moderately stringent conditions includes polypeptides with 10%, 20%, 30%, 40% identity to SEQ ID NO:2 and that the broadly claimed polypeptides comprising fragments of SEQ ID NO:2 read on polypeptides with even less identity to SEQ ID NO:2. Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly

identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). Finally, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally

cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with at least an 80% difference in amino acid composition, function of SEQ ID NO:2 could not be predicted, based on sequence similarity with Bicaudal-D or C-NAP1 nor would it be expected to be the same as that of Bicaudal-D or C-NAP1. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and since the function of the variant polypeptides cannot be determine, one could not predict how to use the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

11. Claims 61 and 63 are rejected under 35 USC 112, first paragraph as the specification does not contain a written description of the claimed invention. The limitation of a polypeptide comprising fragments of (a) or (b) recited in section (c) of claim 61 has no clear support in the specification and the claims as originally filed. A review of the specification reveals support for fragments of Seq ID NO:2 comprising at least 20 or at least 30 contiguous amino acids of SEQ ID NO:2 (p. 14, lines 10-11), but no support for the broadly worded claim. The subject matter

claimed in claims 61 and 63 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 59-61 are rejected under 35 USC 102(a) as being anticipated by Ishikawa et al (DNA Research, 1998 5:169-176).

The claims are drawn to an isolated sGNK polypeptide having a sequence at least 80% identical to SEQ ID NO:2 wherein the polypeptide is capable of binding to and/or being phosphorylated by a GNK polypeptide having the sequence of SEQ ID NO:4.

Ishikawa et al teach a polypeptide with 99% identity to SEQ ID NO:2 (see attached sequence report, us-09-884-001-2.rspt. Although the reference does not specifically state that the polypeptide is capable of binding to or being phosphorylated by a GNK polypeptide, given the identity of the two polypeptides, the claimed invention appears to be the same as the prior art invention. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material structural and functional characteristics of the claimed

product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed polypeptides are functionally different than those taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

15. Claim 63 is rejected under 35 U.S.C. § 103 as being unpatentable over in view of Ishikawa et al, Supra in view of US Patent No. 5,968,781.

The claim is drawn to a sGNK polypeptide including conjugates/oligomers comprising at least one polypeptide according to claim 61. It is noted that the specification teaches that conjugates include fusion proteins derived from recombinant techniques (p. 15, lines 18-20) and that oligomers include fusion proteins comprising multiple polypeptides with or without linkers (p. 18, lines 24-25). Thus, for examination purposes it is assumed that a conjugate/oligomer as claimed includes a fusion protein comprising at least one polypeptide of claim 61 and a different polypeptide.

US Patent No. 5,968,781 teaches a recombinant molecule comprising a polynucleotide encoding a protein which further comprises nucleotide sequences encoding a histidine tag inserted into the 5' terminus or 3' terminus of the gene and further teaches that the tag prevents degradation of the recombinant protein and facilitates purification of the protein by histidine tag affinity column as a metal chelating affinity column (col 3, lines 16-25).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of the Ishikawa et al and US Patent No. 5,968,781 to produce a recombinant protein with a histidine tag because histidine tags are conventionally used to facilitate purification of the recombinant protein. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods of the Ishikawa et al above and US Patent No. 5,968,781 in order to easily recover the expressed

polypeptide and in order to stabilize the protein in solution. Since the fusion polypeptide/conjugate of the combined references comprises both a polypeptide of claim 61 and a different polypeptide, all of the limitations of the claims are met.

16. No Claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
July 14, 2003